Medical Consequences of Cure: Late Effects of Cancer and its Treatment

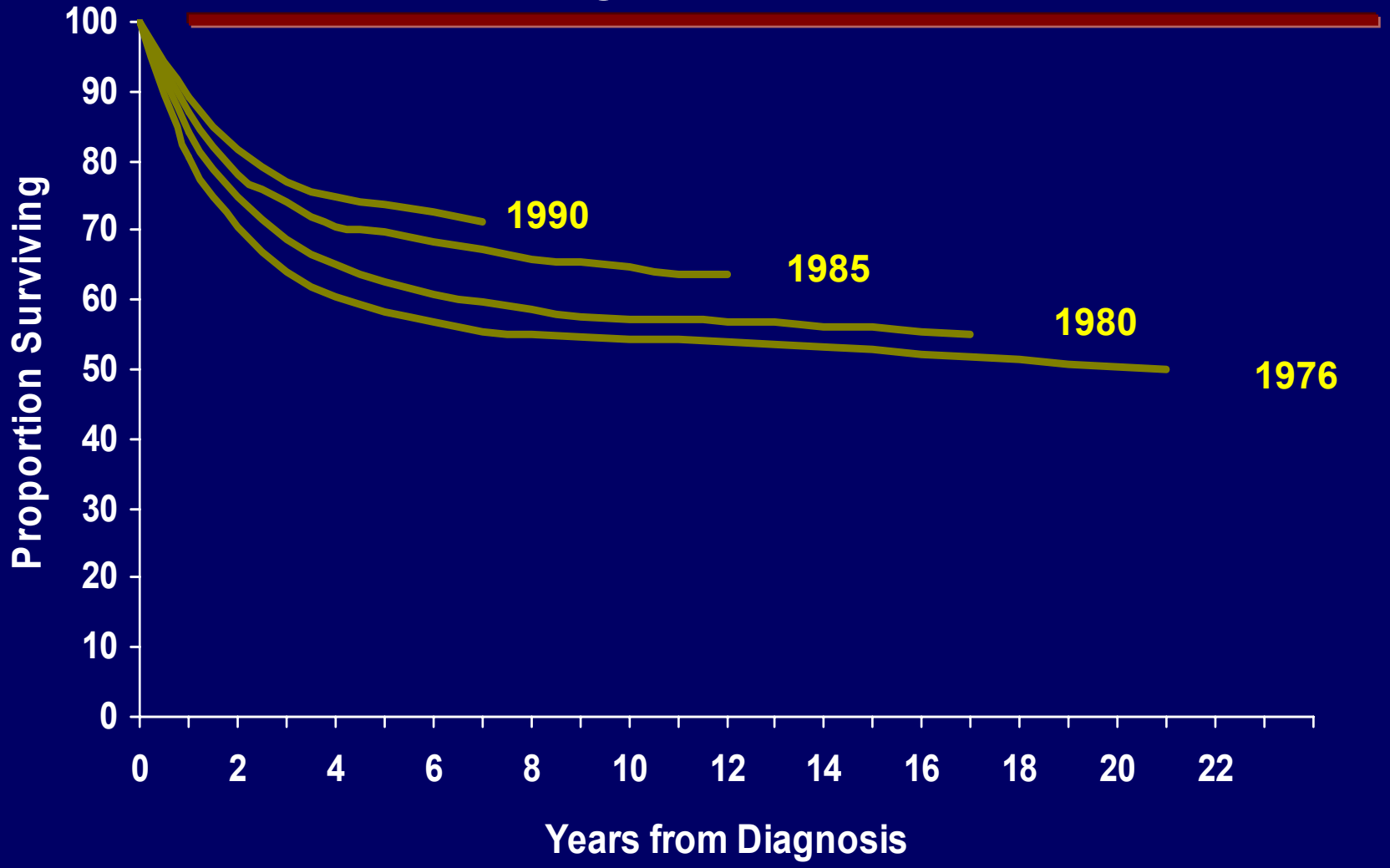
Charles Sklar, MD
Director, Long-Term Follow-Up Program
Memorial Sloan-Kettering Cancer Center
NYC

Supported by NIH grants U24-CA55727 and R01 CA79024

- Cancer is now a curable disease for most individuals
- More than 75% of children, adolescents and young adults diagnosed with cancer will be alive and cancer-free 5 years after diagnosis

Cancer Survival, 0-14 Years of Age

SEER Program 1976-1997



In the U.S. …

- There are more than 250,000 survivors of childhood cancer
- By the year 2010, 1 in 500 young adults will be a survivor of childhood cancer

Types of medical conditions

- Some occur at the time of diagnosis and/or during active treatment (*acute)*
  - *Some go away*
  - *Some may persist*
- Others may not appear for months to years following completion of cancer treatment (*delayed or late effects)*

Overview of late effects

- Spectrum- from mild to life-threatening
- Many can be detected early before there are symptoms or problems
- Many are easily treated
- They include a variety of different types of problems; can affect most organs of the body
- Risk for late effects *determined primarily by one's cancer treatment*
- Risk often *increases with time after* treatment

Late Effects in Survivors of Cancer

Growth and development

- linear growth
- skeletal maturation
- intellectual function
- emotional/social maturation
- sexual development

Vital Organ Function

- Heart
- Lungs
- Kidneys
- Endocrine
- Gastrointestinal
- Vision/Hearing

Fertility and Reproduction

- Fertility
- Health of Offspring

Second Tumors

- Benign
- Malignant

CCSS
Treatment-related mortality

	# deaths	SMR	(95% CI)
Second Cancer	243	16.1	(14.2 -18.2)
Cardiac	86	10.2	(8.2 -12.6)
Pulmonary	33	8.0	(5.6 -11.0)

Mertens et al, JCO 19:3163, 2001

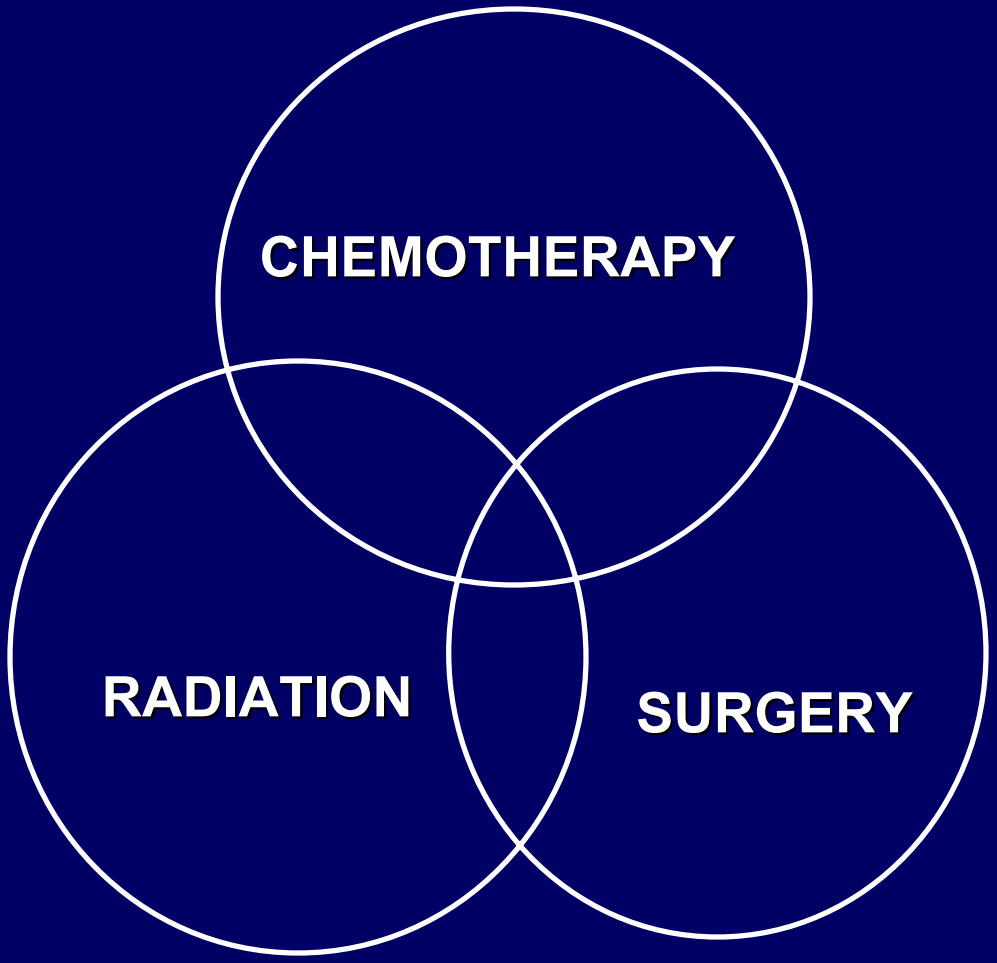
Childhood Cancer Survivor Study (CCSS)

Eligibility Criteria

- Age < 21 years at diagnosis
- Diagnosed between 1970-1986
- Survival 5 years from diagnosis
- Initial treatment at CCSS institution (n=25)
- Includes 14,000 survivors of leukemia, lymphoma, tumors of CNS, bone, soft-tissue, kidney, or neuroblastoma

What are the Major Determinants of Late Effects?

Treatment Factors

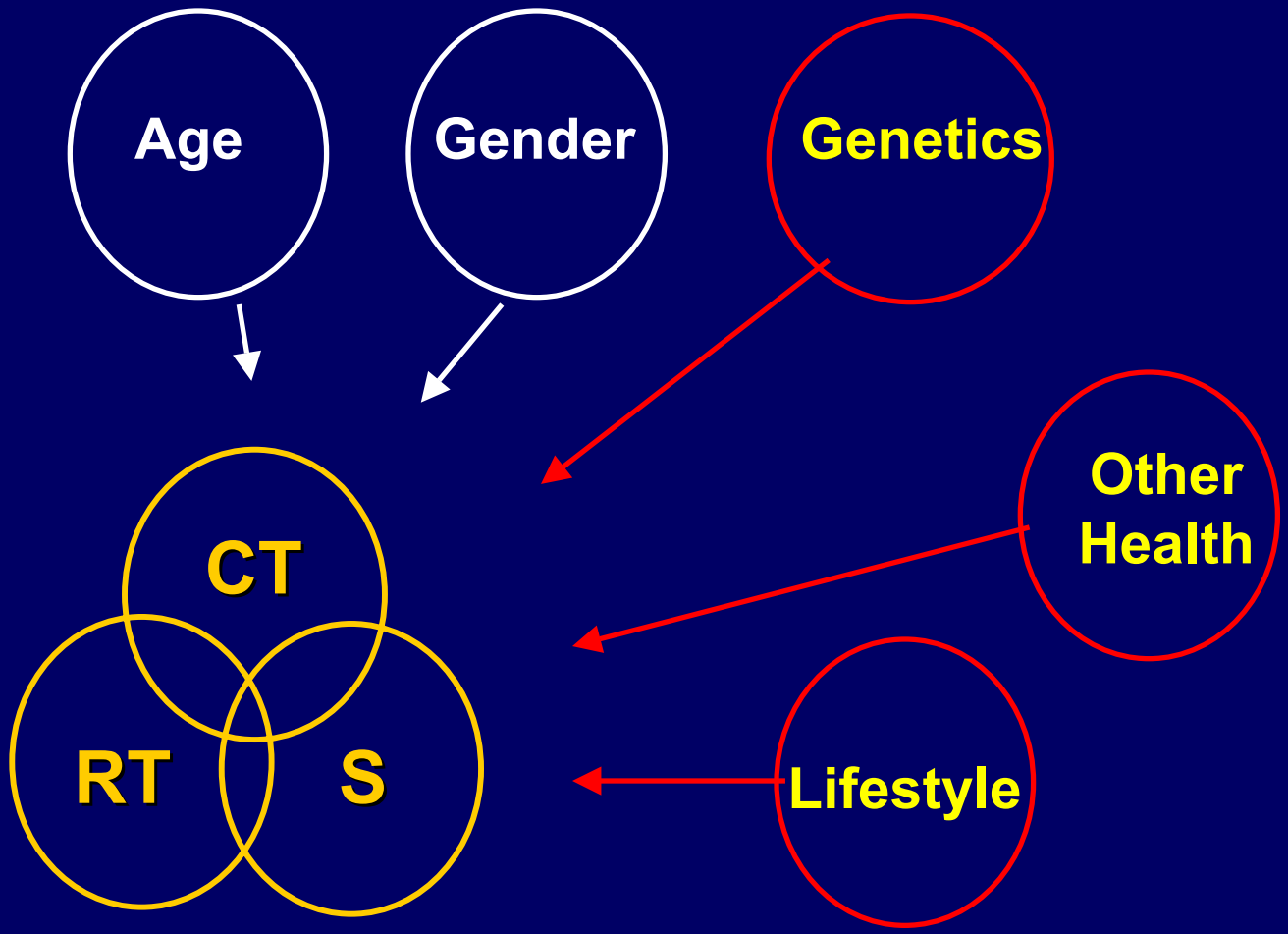


Major Culprits

- RADIATION !!!!!
- Chemotherapy
  - Alkylating agents
  - Topoisomerase II inhibitors
    - Epi podophyllotoxins (eg, etoposide)
    - Anthracyclines

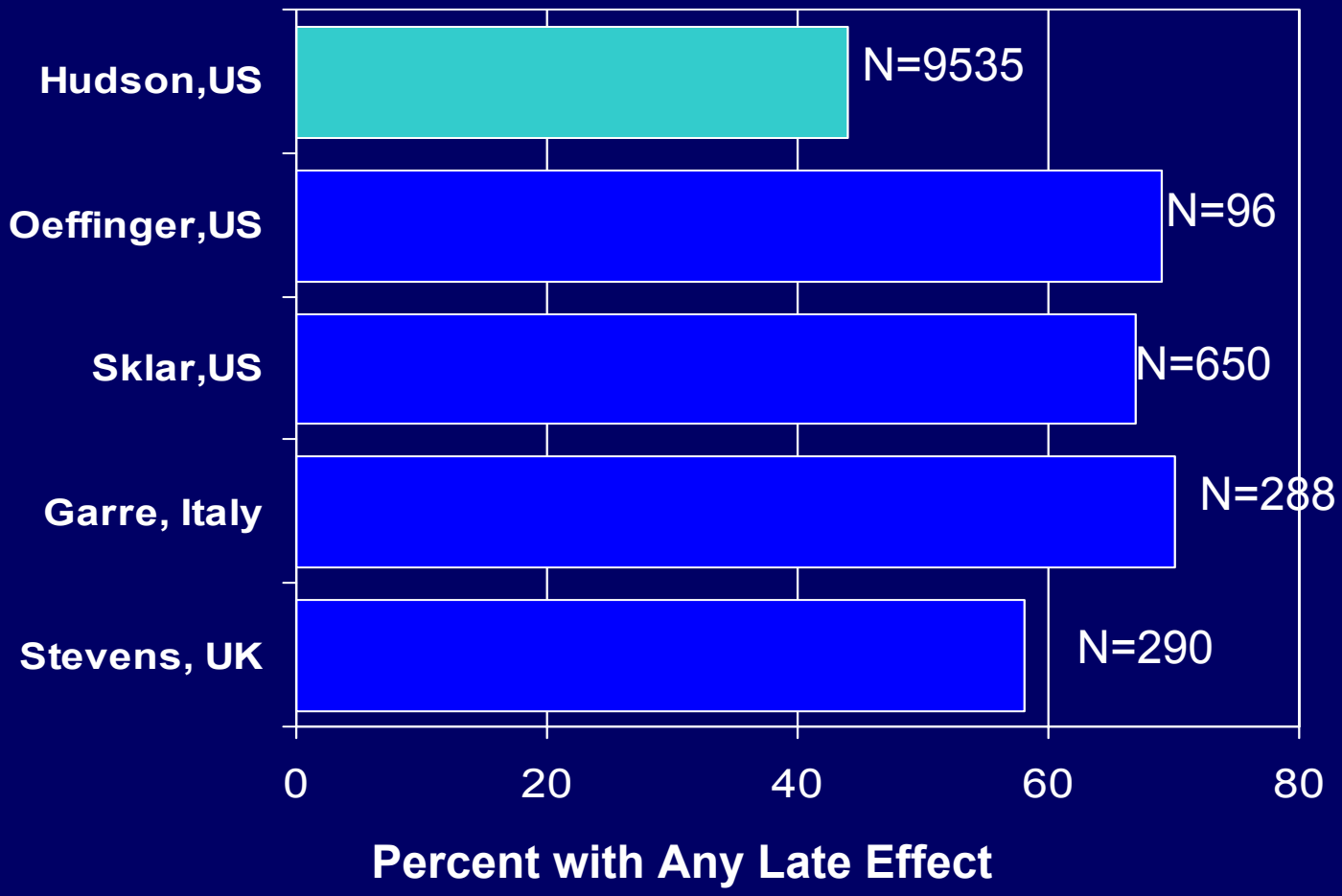
Radiation-induced abnormalities are, in general, both *dose*- and *time*- dependent

Risk Factors to be Considered



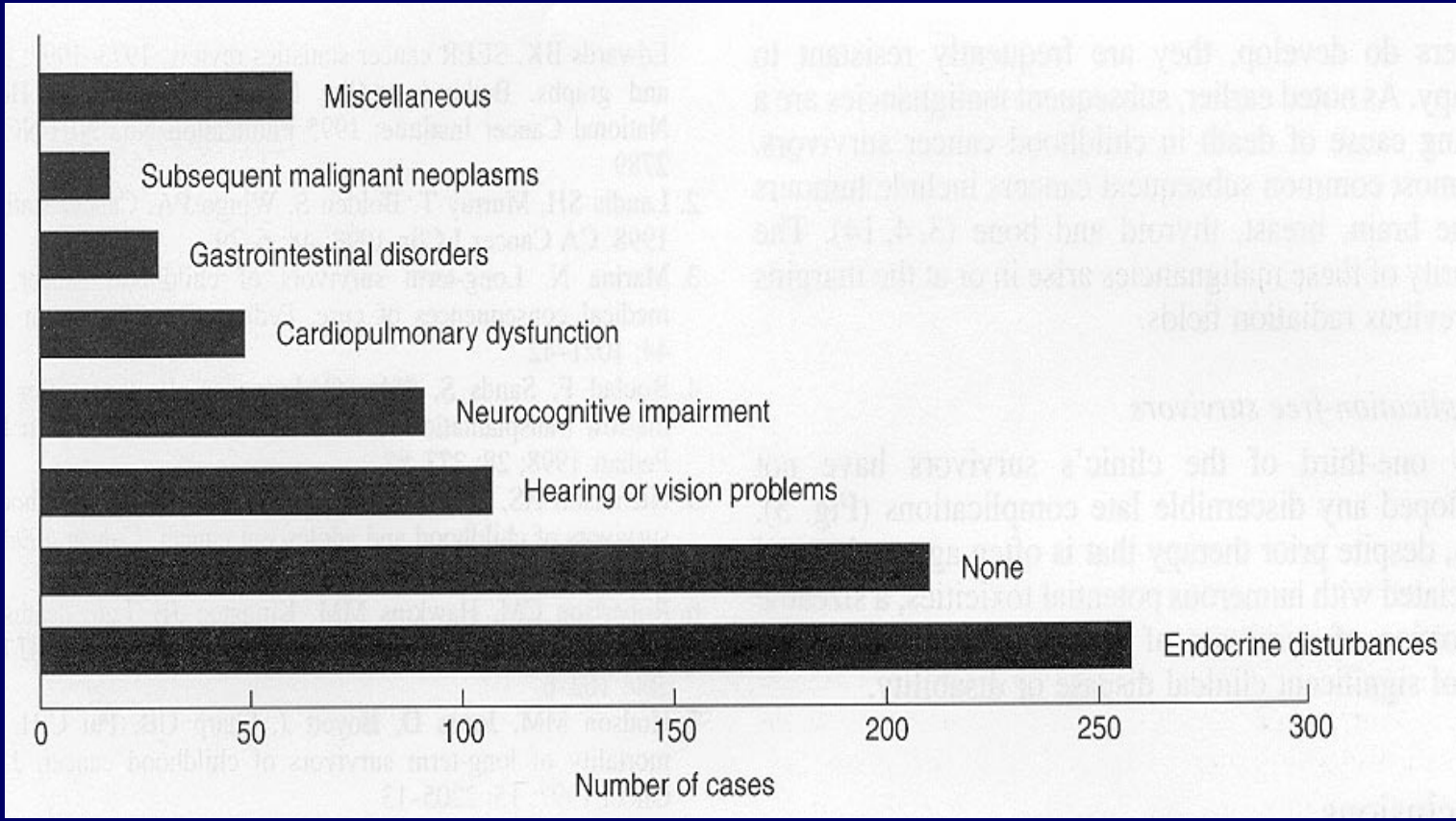
Prevalence and Risk Factors for the most Common Late Effects?

Late Effects in Young Adult Survivors



MSKCC LTFU Clinic

n = 650



Sklar CA. Acta Paediatr Suppl 433:1-4, 1999

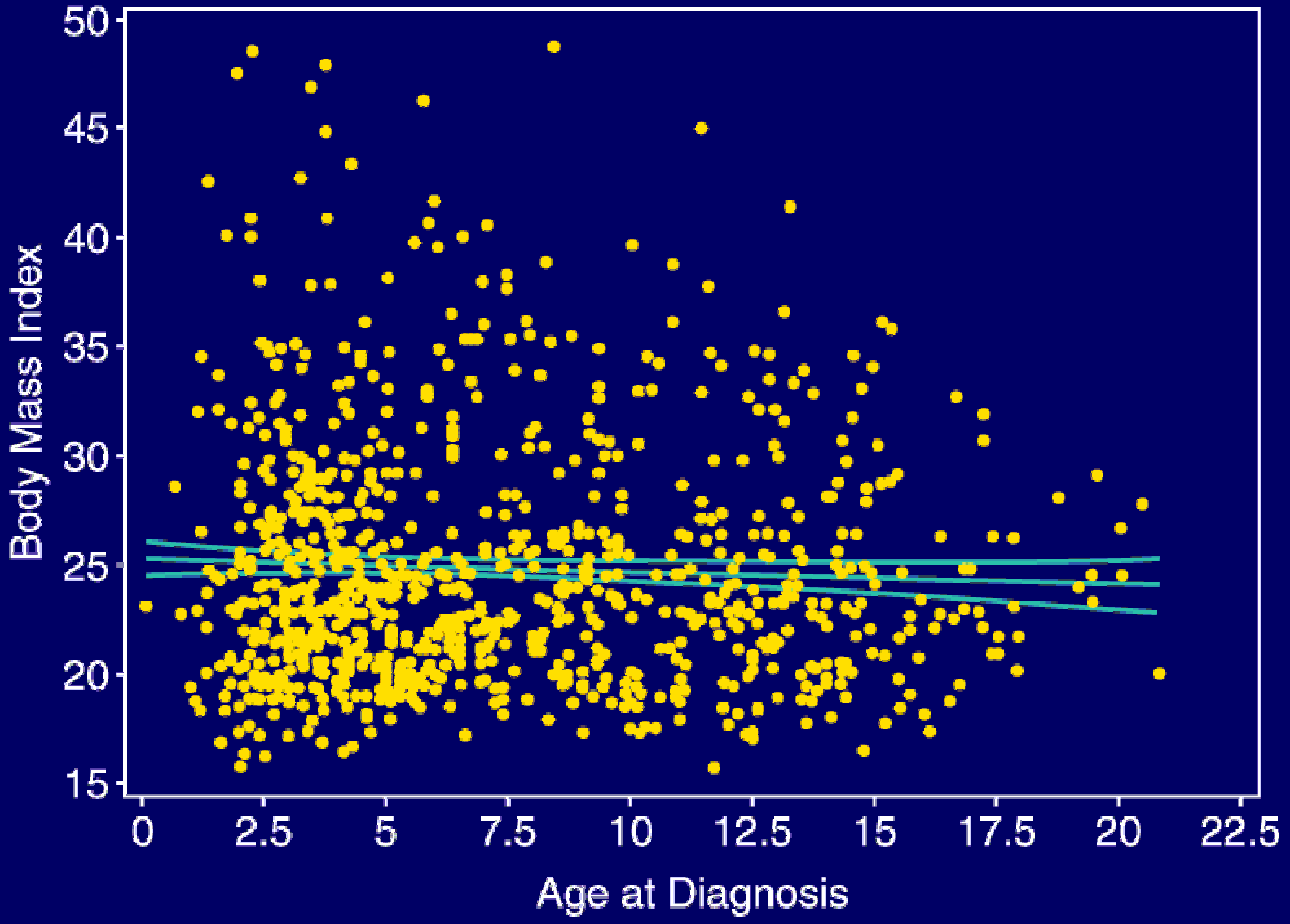
Endocrine and Metabolic Complications

- Most prevalent late effects in survivors of childhood cancer
- Observed in 20-50% of survivors followed into adulthood
- Most often seen in survivors of:
  - Stem cell/bone marrow transplant
  - Brain tumors
  - Hodgkin's disease

Endocrine and Metabolic Complications

- Hypothalamic-pituitary abnormalities
  - GH*, TSH, LH/FSH, ACTH deficiencies
  - Precocious puberty*
  - Abnormal BMI
- Thyroid abnormalities
- Gonadal dysfunction
  - Sex hormone deficiency
  - Infertility
- Insulin-resistance/metabolic syndrome

Female Survivors of ALL Treated with ≥ 20 Gy CRT



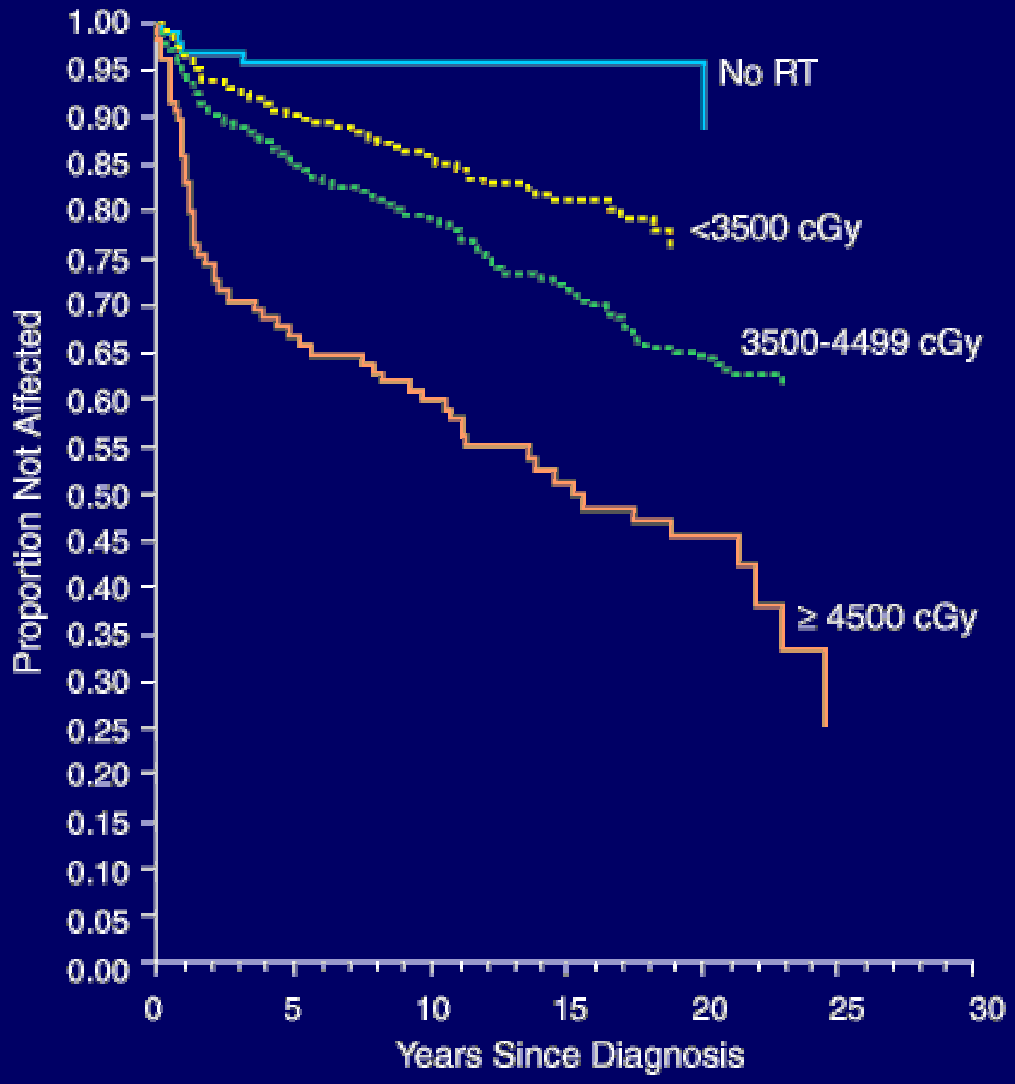
Oeffinger et al, JCO 21:1359, 2003

Risk Factors for Underactive Thyroid

Covariate	RR (95% CI)	P Value
Radiation dose to thyroid:		
<3500 cGy	3.8 (1.7 to 10.8)	0.004
3500-4499 cGy	5.5 (2.5 to 15.3)	0.0002
≥4500 cGy	10.7 (4.7 to 30.6)	<0.0001
Time since dx < 5 yrs	2.1 (1.7 to 2.6)	<0.0001
Female sex	1.7 (1.4 to 2.1)	<0.0001
Age at dx >15 yrs	1.5 (1.2 to 1.9)	0.0001

Sklar et al, JCEM 85:3227, 2000

HYPOTHYROID IN HD



Sklar et al, JCEM 85:3227, 2000

Childhood Cancer Survivor Study

Pulmonary Complications in Survivors

(N=12,390)

5+ years post diagnosis*

	Relative Risk (95% CI)	
Siblings	1.0	
Lung fibrosis	**3.4**	**(2.1 - 5.5)**
Pneumonia, 3+ times	**4.9**	**(2.6 - 9.2)**
Chronic cough,	**2.3**	**(1.9 - 2.8)**
Pleurisy	**1.4**	**(1.1 - 1.8)**
Supplemental oxygen	**3.0**	**(2.5 - 3.7)**

*adjusted for sex, smoking status

Mertens et al, Cancer 95:2431, 2002

Risk Factors for Pulmonary Dysfunction

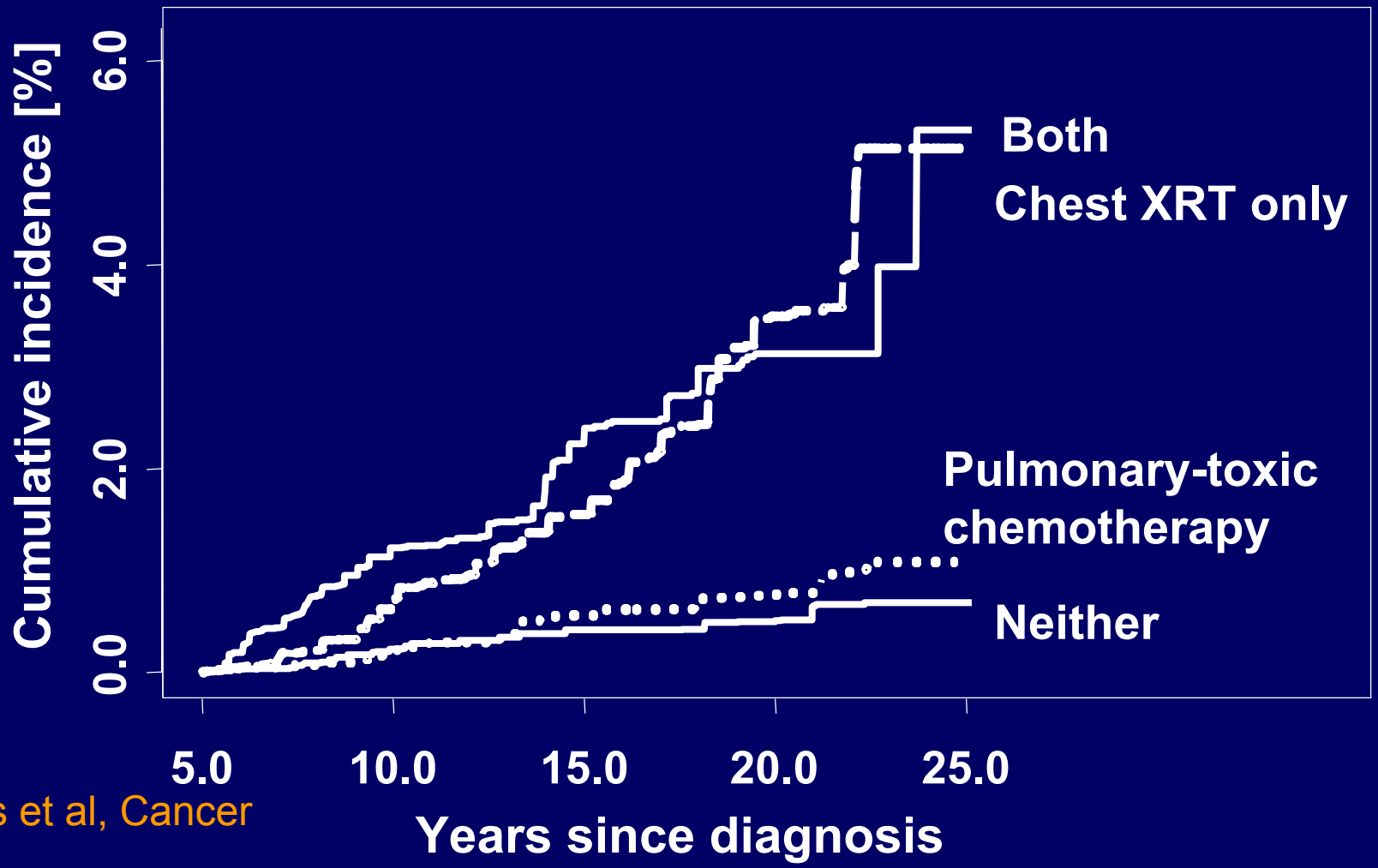
- Chest Radiation
- Bleomycin
- Busulfan
- Cyclophosphamide
- BCNU

Mertens et al, Cancer 95:2431, 2002

Childhood Cancer Survivor Study

Pulmonary Complications in Survivors

Cumulative Incidence of Lung Fibrosis



Mertens et al, Cancer 2002

Cardiotoxicity

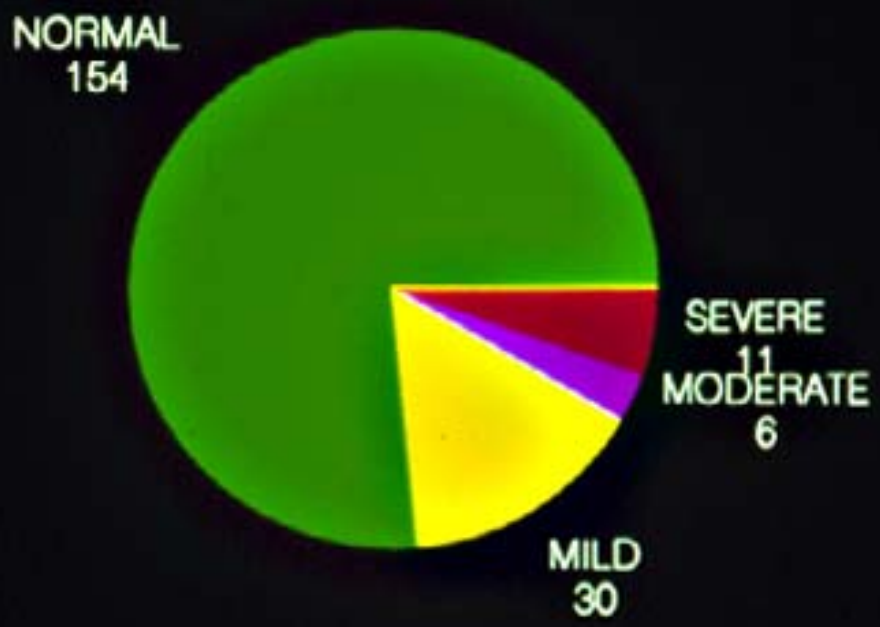
- Heart Muscle
- Conducting System
- Pericardium
- Coronary Blood Vessels
- Heart Valves

Risk Factors for Late Cardiac Toxicity

- Treatment factors
  - Anthracycline Dose (> 300 mg/m^2)
  - Chest RT
  - Acute cardiotoxicity during treatment
- Host factors
  - Younger Age
  - Female Gender
- Lifestyle factors
  - Heavy weight lifting
  - Cocaine use
  - Labor & delivery

SEVERITY OF MYOCARDIAL DYSFUNCTION

Steinherz et al, JAMA 1991



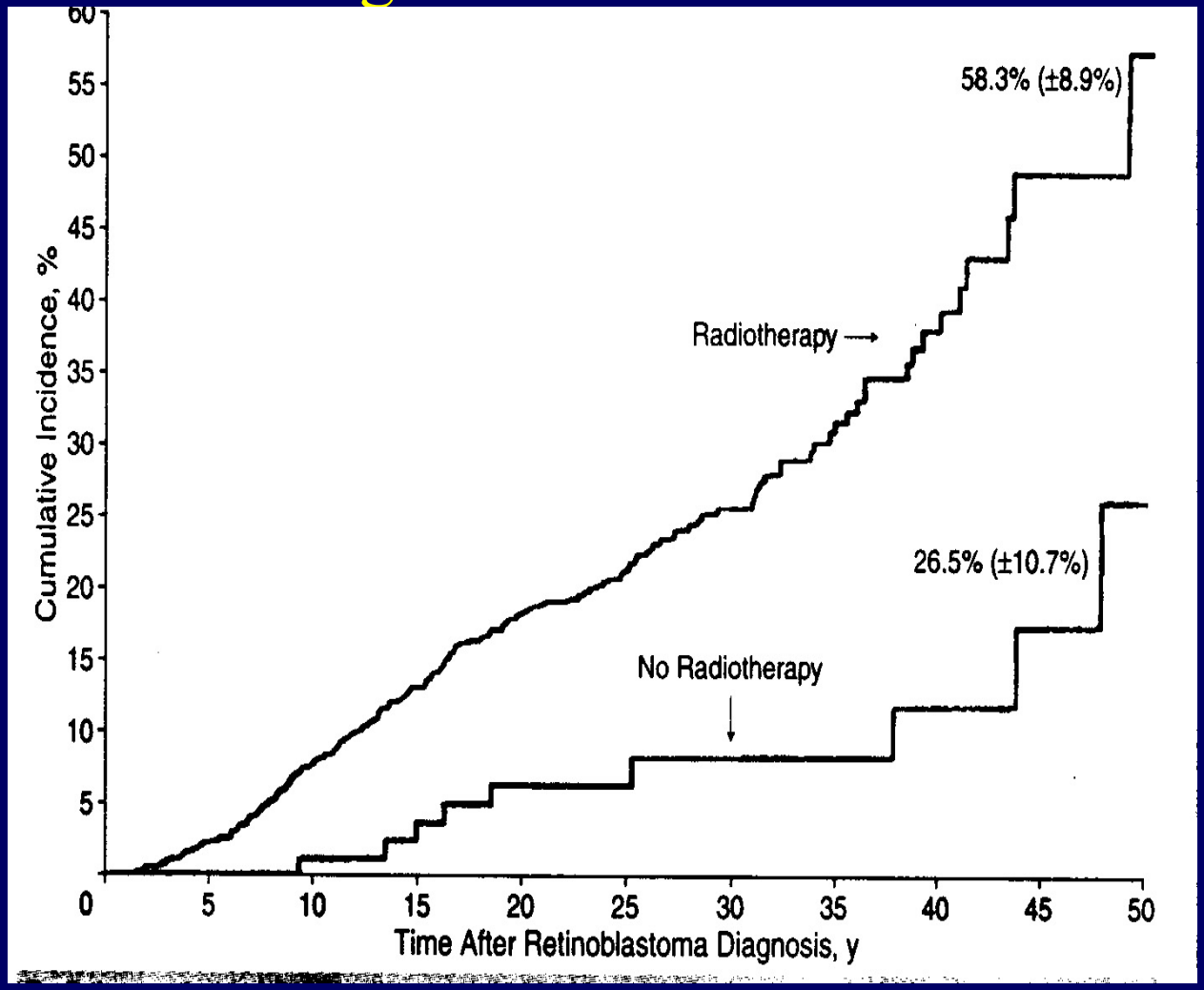
47/201 = 23% ABNORMAL AT LTFU

Risk Factors for SMN

- Treatment
  - Radiation
  - Chemotherapy
    - Alkylating agents
    - Topoisomerase II inhibitors
- Host Factors
  - Young age at treatment
  - Female gender
  - RB germline mutations
  - Polymorphism in gene for enzyme thiopurine S-methyltransferase (TPMT)
- Lifestyle Factors
  - smoking

SMN's in Bilateral RB

Wong et al. JAMA 1997



Conclusions

- Survivors of childhood cancer are at increased risk of developing late abnormalities of various vital organs
- Numerous studies have worked out the major treatment effects
- Paucity of data on outcomes in minority populations and in survivors beyond 4th decade of life
- Future studies will need to examine the interaction between treatment, genetics, medical co-morbidities, and life-style choices
- Additional studies are needed in order to develop interventions that will eliminate or reduce these risks

CCSS Participating Institutions

University of California-San Francisco
University of Alabama
International Epidemiology Institute
University of Washington
UT-Southwestern Medical Center at Dallas
Dana-Farber Cancer Institute
Texas Children's Center, Houston
Children's Hospital and Medical Center, Seattle
Roswell Park Cancer Institute
Hospital for Sick Children, Toronto

St. Louis Children's Hospital
St. Jude Children's Research Hospital
University of Michigan
Stanford University School of Medicine
Children's Hospital of Philadelphia
Children's Hospital, Oklahoma City
Children's Hospital, Denver
Children's Health Care-Minneapolis
Columbus Children's Hospital
Children's National Medical Center, Washington, DC
Children's Hospital of Pittsburgh
University of Minnesota
Cincinnati Children's Hospital Medical Center
Children's Hospital Los Angeles
Memorial Sloan-Kettering Cancer Center
National Cancer Institute
Mayo Clinic
U.T.M.D. Anderson Cancer Center
Riley Hospital for Children
Fred Hutchinson Cancer Research Center
University of California-Los Angeles